UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/566,410	05/29/2007	Deborah Hurst	PAT051920-US-NP02	5534

20855 7590 10/01/2010

ROBINS & PASTERNAK
1731 EMBARCADERO ROAD
SUITE 230
PALO ALTO, CA 94303

EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
10/01/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

ADVSIORY ACTION

Claims 1, 6-8, 13-15 are examined in the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 6-8, 13-15 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Wierda et al, 2001, Expert Rev Anticancer Ther, 1(1): 73-83, IDS of 4/19/07, in view of Dmoszynska et al, 1999, Leukemia & Lymphoma, 34(3-4): 335-340, IDS of 04/17/09, and Denis-Mize et al, 2003, J Immunother, 26 (6), S43, abstract only, of record, an further in view of Mark et al (US 4,518,584, filed on 12/20/1983), and as evidenced by the instant specification (p.3), for reasons already of record in paper of 7/27/10.

The response asserts as follows:

In particular, Wierda discusses the use of Campath-1H as an immunotherapeutic agent for treating CLL. The Office has acknowledged on the record that Wierda does not teach the combination of aldesleukin and Alemtuzumab, and the administration schemes presented in the dependent claims. See, Office Action dated February 17, 2010, page 4. Additionally, Wierda does not relate to the use of concurrent combination therapy for treating CLL.

Dmoszynska, like Wierda, also does not pertain to the use of concurrent combination therapy for treating CLL, as claimed. Rather, Dmoszynska relates to the use of IL-2 in patients previously treated with the chemotherapeutic agent 2 CdA. There is no discussion whatsoever regarding the use of IL-2 with antibody therapy. Chemotherapeutic agents and antibodies are hardly the same and have completely different mechanisms of action. There is no reason to expect that substituting an antibody such as Alemtuzumab for a chemotherapeutic agent would provide an equivalent response.

Mark, as with the other cited art, also does not pertain to concurrent, combination therapy. In fact Mark does not relate to cancer treatment of any kind, let alone treatment of CLL and merely describes the production of aldesleukin.

As previously pointed out to the Examiner, the only art cited that relates to combining IL-2 therapy with an antibody is Denis-Mize. Denis-Mize does not specify that the patients suffered from CLL and, importantly, Denis-Mize did not use Alemtuzumab but rather Rituximab. These two antibodies are not analogous and therefore cannot be expected to provide analogous responses. The antibodies are directed against different surface antigens and therefore bind to different ligands. The two antibodies are unrelated and the efficacy of substituting one antibody for the other is not predictable.

The Examiner disputes this argument, stating: "One would have a reasonable expectation of a successful therapy of CLL using the method of the cited combined art, in view that a combination of IL-2 with an anticancer drug or antibody has been shown to be successful for treating cancer, in view of the teaching of Dmoszynska et al. and Denis-Mize et al, of record." However, this argument completely ignores the fact that none of the cited art teaches concurrent

therapy as claimed and, importantly, a chemotherapeutic agent, such as described in Dmoszynska and the antibody described in Denis-Mize are simply not analogous, either structurally or functionally, to Alemtuzumab. There would be no reason to expect that the use of a completely different molecule in combination with IL-2 using a different treatment regimen would elicit the same results.

The response has been considered but is not found to be persuasive for the following reasons:

Applicant argues individual references.

Further, one would have a reasonable expectation of success, because of the following reasons: Although a chemotherapeutic agent, such as described in Dmoszynska and the antibody described in Denis-Mize are not analogous, either structurally or functionally, to the antibody Alemtuzumab, one would have expected that IL-2 would increase T cells and NK activity in the combination therapy of IL-2 with the antibody Alemtuzumab, and would be successful in treating CLL by complementing the action of Campath et al, in view that: 1) CLL patients have defective T-cell or NK-cell mediated immunity as taught by Wierda et al, which defective immunity is further suppressed by treatment with Campath, as taught by Wierda et al, 2) It is the property of IL-2 to increase T cells and NK activity and IL-2 is successful in treating cancer in both combination therapies of IL-2 with the antibody rituximab in lymphoma patients, in which IL-2 enhances NK-mediated cytolytic killing and augments ADCC, as taught by Denis-Mize or with 2CdA in CLL patients, as taught by Dmoszynska et al, and 3) Campath by itself has been used successfully for treating CLL as taught by Wierda et al. It is noted that Campath is the same as Alemtuzumab, as evidenced by the instant specification.

The response asserts as follows:

Furthermore, the Examiner continues to assert that applicants merely determined "optimum concentration 0f reactants." However, as previous explained, the claimed method is not merely "optimization" that one of skill in the art achieved through "routine experimentation." The skilled artisan simply could not predict that a treatment regimen as claimed would indeed be efficacious. Cancer therapy is extremely complex and it is well known that the timing of administration is critical.

The response has been considered but is not found to be persuasive for the following reasons:

Applicant has not shown that the claimed timing of administration would produce result superior than the optimization of the timing of administration known in the art, such as the timing of administration of IL-2 and 2CdA taught by Dmoszynska et al, in which IL-2 is given daily at low dose between the courses of 2CdA, and patients are given 3-6 cycles of 2CdA (p.336, first column), and/or the timing of administration of IL-2 and the antibody rituximab, in which the antibody is administered on day 0, and IL-2 is administered on day 8, 15, 22 and 36, as taught by Denis-Mize et al. To determine optimum concentration of reactants is within the level of ordinary skill in the art. See *In re Kronig*, 190 USPQ 425, and because "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See also *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

The response asserts as follows:

Additionally, the Office disputes applicants' arguments regarding the possibility of drug-drug interactions in combination therapy that can result, inter alia, in a non-existent or diminished effect of one or both of the agents, or the appearance of new effects not seen with either drug alone. Applicants previously submitted Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 10th Edition, McGraw-Hill Publishing Division, 2001, pages 54-56 which clearly supports the proposition that the efficacy of two agents in combination, such as aldesleukin and Alemtuzumab, is unpredictable. The Examiner has provided no evidence to the contrary.

The Office states applicants have not "provided any reference showing a severe toxicity due to the particular interaction between IL-2 and the anti-CD52 antibody taught by the combined art." However, such art is not possible to provide as there does not appear to be prior art directed to the use of applicants, claimed method.

The response has been considered but is not found to be persuasive for the following reasons:

Concerning the severe toxicity due to possible drug-drug interaction, Applicant has not provided any evidence showing a severe toxicity due to the particular interaction between IL-2 and the anti-CD52 antibody taught by the combined art. On the contrary, IL-2 combined with an anti-cancer monoclonal antibody, rituximab, has been used successfully for treating a lymphoma, as taught by Denis-Mize et al, of record. Further, it is noted that this a not a FDA review, and thus the FDA standard such as severe toxicity is not germane here.

The response asserts as follows:

Applicants continue to assert the combination cited by the Office does not provide evidence that the claimed invention is a "predictable use of prior art elements according to their established functions" (*KSR Int'l Co. v. Teleflex, Inc.*, 82 USPQ2d 1385, 1396 (U.S. 2007)) Rather, as explained above, the evidence is to the contrary.

Additionally, it is axiomatic that statements in the prior art must be considered in the context of the teaching of the entire reference, and a rejection of claims cannot be predicated on mere identification in a reference of individual components of claimed limitations. In this regard, the Federal Circuit has consistently reversed a finding of obviousness, even when all claimed elements are individually present in the references. See, e.g., In re Kotzab 217 F.3d 1365, 55 USPQ2d 1313, 1317 (CAFC 2000, emphasis added).

Virtually all inventions are combinations of elements that can be individually identified in multiple references. See, e.g., *In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998), noting that the Office cannot rely on a high level of skill in the art to overcome the differences between the selected elements in the references, it cannot rely on a high level of skill in the art to provide the necessary motivation; *In re Lee*, 61 USPQ2d 1430 (Fed. Cir. 2002), affirming that common knowledge and common sense are not the specialized knowledge and expertise necessary to establish a motivation to arrive at the claimed invention.

Thus, the requirement is not whether each claimed element can be identified individually in a reference but, rather, whether the Examiner can show "reasons that the skilled artisan, confronted with the same problem as the inventor, and with no knowledge of the claimed invention, would select the elements from the cited prior art reference for combination in the

manner claimed." *In re Rouffet*, 47 USPQ2d at 1458. In the pending case, the Office has not met this burden.

Without a suggestion to modify the references evident in the prior art, as well as a lack of a reasonable expectation of success, the only conclusion supported by the record is that the rejection was made impermissibly using hindsight reconstruction of the invention.

The response has been considered but is not found to be persuasive for the following reasons:

One would have motivated to combine IL-2 with Campatth, because CLL patients have defective T-cell or NK-cell mediated immunity as taught by Wierda et al, which defective immunity is further suppressed by treatment with Campath, as taught by Wierda et al, and because IL-2 increases T cells and NK activity in combination therapies of IL-2 with either the antibody rituximab in lymphoma patients, as taught by Denis-Mize or with 2CdA in CLL patients, as taught by Dmoszynska et al. Further, Denis-Mize et al teach that a combination with IL-2 would improve the efficacy and durability of anti-cancer monoclonal antibody therapy (abstract, first two lines).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, MISOOK YU can be reached on 571-272-0839. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MINH TAM DAVIS
September 29, 2010

/Misook Yu/
Supervisory Patent Examiner, Art Unit 1643